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Pd(II)-Catalyzed Intramolecular Amidoarylation of Alkenes with Molecular Oxygen as Sole Oxidant

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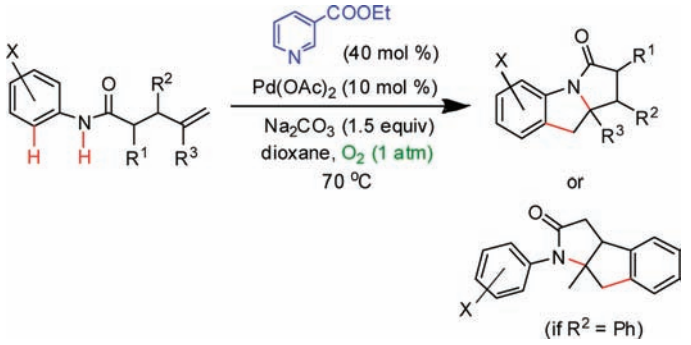
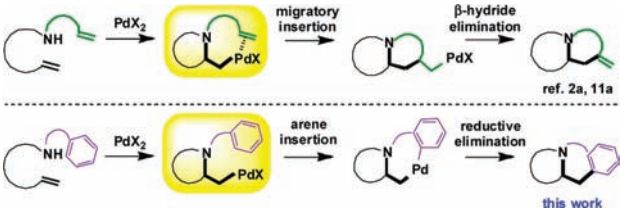
ABSTRACT



Stereoselective palladium-catalyzed synthesis of structurally versatile indoline derivatives, using molecular oxygen as the sole oxidant, is described. New C−N and C−C bonds form across an alkene in an intramolecular manner. The C−N bond-forming step proceeds *via* a *syn*-amidopalladation pathway. The moderate kinetic isotope effects (intramolecular KIE = 3.56) suggest that electrophilic aromatic substitution occurs in the arylation step.

Oxidative functionalization of alkenes has emerged as a rapid, selective, and versatile bond-forming strategy, thereby offering opportunities to advance chemical synthesis and address the increasing demands for economical and sustainable synthetic methods. Over the past few decades, significant progress has been made on the selective construction of carbon−heteroatom bonds across an alkene by utilizing transition-metal catalysis.[1] Selective difunctionalization methods of forming both C−C and C−X bonds across an alkene are of great potential to the rapid construction of molecular complexity in the context of biologically relevant heterocyclic architectures. With the poineering works established by Hegedus[2] and Semmelhack,[3] nucleopalladation of alkenes became a versatile entry to new C−C bond formation in the presence of CO or an alkene/alkyne. However, the analogous bond-forming events that involve an arene as the coupling partner are relatively uncommon, partly because of the general inertness of the aromatic system and the need of arene-activation mechanisms.[4]

Scheme 1. Alternative Strategy of Multibond-forming Cyclization



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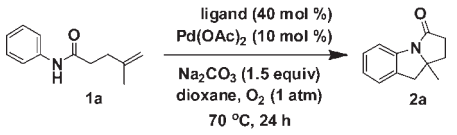
Recently, Wolfe developed carboamination reactions between aryl bromides and aminoalkenes.[5] Chemler established the copper-catalyzed double cyclization of aminoalkenes through intramolecular arylation with an alkyl radical generated *in situ* from a Cu−C bond.[6] Michael reported the intermolecular carboamination of alkenes with unactivated arenes through a Pd^{II}/Pd^{IV} catalytic manifold.[7] Zhang and Toste independently demonstrated intramolecular carboamination between arylboronic acid and aminoalkenes *via* Au^{I}/Au^{III} catalytic cycles.[8] However, these strategies inevitably require either stoichiometric external oxidants, which are transition-metal or organic reagents, or preactivated reactants for completing the catalytic cycle. Molecular oxygen is regarded as an ideal oxidizing agent because it is abundant in the atmosphere and benign to the envirnoment, and redox reactions coupled with it would not lead to waste treatment issues.[9,10] In this regard, our group has pursued the development of palladium-catalyzed functionalization of alkenes, under simple aerobic conditions, as an efficient multibond-forming cyclization strategy for rapid access to a wide array of ring scaffolds (Scheme 1),[11] which represent core structures of biologically important pyrrolizidine and mitomycin alkaloids.[12] Herein we report the palladium-catalyzed intramolecular amidoarylation of alkenes using 1 atm of molecular oxygen as the sole oxidant.

As shown in Table 1, the cyclization reaction of **1a** to yield **2a** is dependent on the nature of the ligand. For instance, triphenylphosphine was not suitable since it was susceptible to oxidation (entry 1). Ligand screening was then focused on *N*-heteroaromatics, owing to its easy availability, structural diversity, and tolerance to oxidants.[11c] Pyridine and various benzo-fused pyridine analogs only led to modest yields (entries 2−5). Substantial improvements were made when the 3-position, rather than the 4- and 2-positions, of the pyridine core was substituted with an electron-withdrawing group (entries 6−8). 3-Acetylpyridine resulted in moderate yield (entry 9). Gratifyingly, ethyl nicotinate[13] was identified as the superior ligand (entry 10). Lowering the ligand loading was deleterious to the cyclization (entries 11−13). The use of a slight excess of sodium carbonate as the base was beneficial to improve the yields (entries 14−16).

This intramolecular amidoarylation reaction is applicable to a variety of aromatic systems (Scheme 2). On *para*-substituted arene systems, electron-deficient anilides

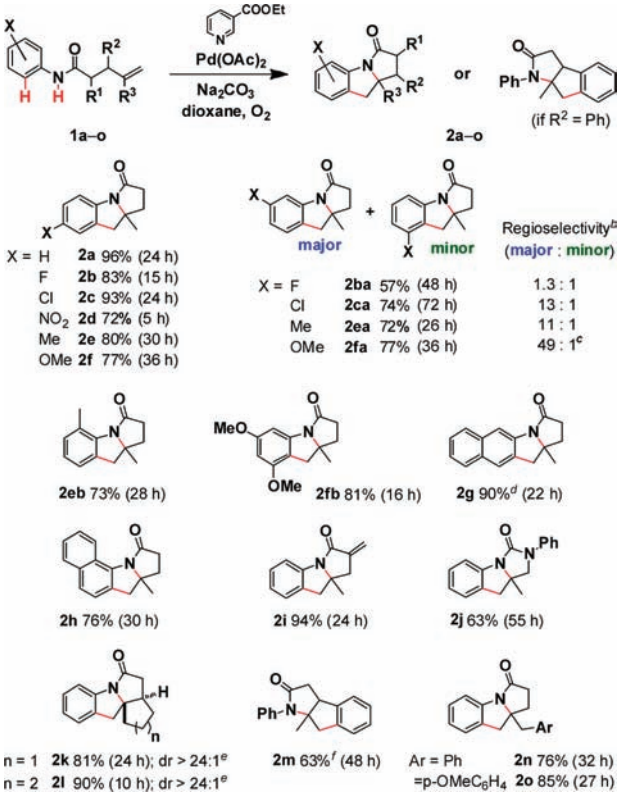
Table 1. Optimization of Reaction Conditions[a]



entry	ligand	% yield[b]	entry	ligand	% yield[b]
1	PPh_3	5	9	3-acetylpyridine	51
2	pyridine	58	10	ethyl nicotinate	83
3	quinoline	44	11[c]	ethyl nicotinate	79
4	isoquinoline	55	12[d]	ethyl nicotinate	28
5	acridine	20	13	–	15
6	2-cyanopyridine	6	14[e]	ethyl nicotinate	82
7	3-cyanopyridine	44	15[f]	ethyl nicotinate	80
8	4-cyanopyridine	22	16[g]	ethyl nicotinate	66

[a] Reaction conditions: 0.2 mmol of substrate **1a**, 40 mol % of ligand, 10 mol % of $Pd(OAc)_2$, 1.5 equiv of Na_2CO_3, 1 atm of O_2, 2 mL of dioxane, 70 °C, 24 h. [b] Determined by ^1H NMR using nitrobenzene as the internal standard. [c] 20 mol % of ethyl nicotinate. [d] 10 mol % of ethyl nicotinate. [e] 1.0 equiv of Na_2CO_3. [f] 0.5 equiv of Na_2CO_3. [g] In the absence of Na_2CO_3.

Scheme 2. Oxidative Double Cyclization[a]



[a] Unless otherwise indicated, all reactions were performed at 70 °C with substrate (0.3 mmol), ethyl nicotinate (40 mol %), Na_2CO_3 (1.5 equiv), and $Pd(OAc)_2$ (10 mol %) in dioxane (3 mL) under 1 atm of O_2. [b] Determined by ^1H NMR analysis of the crude reaction mixtures. [c] Determined by LCMS analysis. [d] Minor regioisomer was obtained in 2% yield. [e] Diastereomeric ratios were determined by ^1H NMR analysis of the crude reaction mixtures. [f] Indoline-type cyclization product was obtained in 23% yield.

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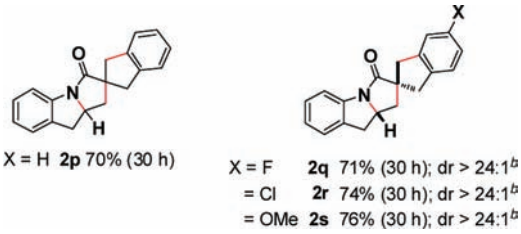
(**1b**–**d**) cyclize faster than did their electron-rich counterparts (**1e**–**f**). The regioselectivity issue of amidoarylation arises from anilides having two sterically distinct aryl C–H bonds for cyclization: on the *meta*-substituted anilide system, **2ba** was formed as a mixture of regioisomers (1.3:1) in 57% yield. Notably, the regioselectivities improved significantly in other *meta*-substituents (13:1 for Cl; 11:1 for Me; 49:1 for OMe). Despite steric crowding with the amide carbonyl, *ortho*-substituted arenes such as **2eb** could also be obtained in good yields. Interestingly, the cyclization of *meta,meta*-dimethoxy-substituted anilide, leading to **2fb**, was even faster than that which formed **2fa**. On the other hand, the highly regioselective amidoarylation took place on the naphthyl ring system, guided by the ease of forming corresponding palladacycles, leading to the formation of **2g** and **2h**, respectively.

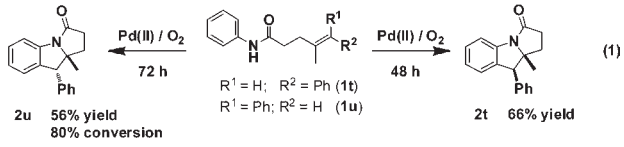
Indoline **2i** was produced in 94% yield and the delicate α,β-unsaturation unit was tolerated, reflecting the mildness of the reaction conditions. In comparison with previous methods developed by Hegedus[2a] and us,[11a] the present strategy of accessing related indoline skeletons is superior in both product yield and reaction rate. Upon amidoarylation, a nitrogen-tethered olefin furnished cyclic urea **2j**. Tricyclic fused frameworks **2k** and **2l** could be established from exocyclic olefins of various ring sizes. Notably, pyrrolidine-related ring scaffold **2m** was formed in 63% yield upon selective arylation with a β-phenyl ring, instead of an N-substituted arene. However, the exclusive formation of **2n** and **2o** and the inertness of the δ-arenes implied that the electronic property of the arene is not the controlling factor in the cyclization.

Since the oxidative cascade cyclization represents a rapid and economical strategy to construct polycyclic systems, we extended the scope of amidoarylation to oxidative triple cyclization (Scheme 3). Cyclization of *o*-allyl anilide **1p** proceeded through sequential amidopalladation/olefin insertion/arylation events to give **2p** in 70% yield *(equivalent to 89% yield per bond formation)*. Importantly, cascade cyclizations are highly diastereoselective for establishing spiro-ring frameworks **2q**–**s** upon the formation of three bonds and two chiral centers (one of which being a quaternary center) in a single step in good yields.

Scheme 3. Oxidative Triple Cyclization[a]



[a] The reaction conditions are identical to those mentioned in Scheme 2. [b] Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures.



In contrast to common nitrogen nucleophiles such as arylsulfonyl amides, anilides in possession of a less acidic N–H bond are less prone to undergo transition-metal-assisted N–H deprotonation, a prerequisite step of *syn*-nucleopalladation. As a result, studying the stereochemical outcomes of the amidoarylation reaction may shed light on the mechanistic details. The Pd-catalyzed amidoarylation of *E*-alkene **1t** furnished **2t** selectively in 66% yield (eq 1). On the other hand, cyclization of *Z*-alkene **1u** led to the exclusive formation of **2u**, thereby supporting a *syn*-amidopalladation as the cyclization pathway.[11d,14]

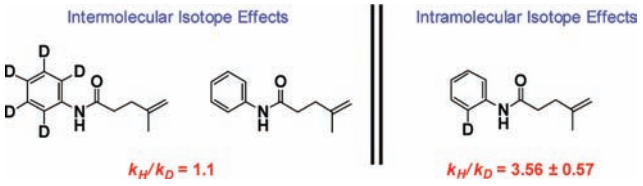


Figure 1. Deuterium kinetic isotope effects.

The low value of the intermolecular kinetic isotope effect (k_H/k_D) indicates that the C–H bond-breaking step occurs

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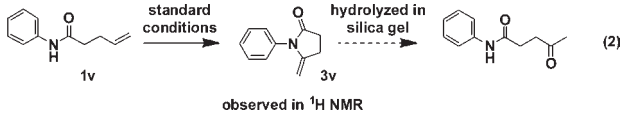
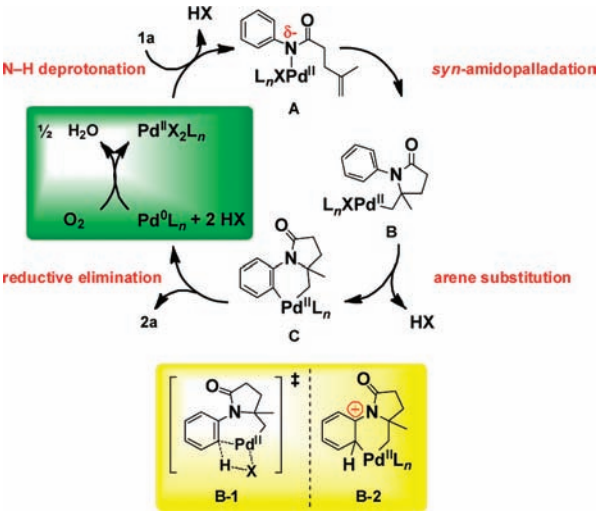
after the turnover-limiting step (Figure 1). The observed intramolecular KIE of 3.56 (average of 4 runs) is in the normal range of electrophilic palladation of arenes.[15] The fact that electron-deficient anilides (e.g., *p*-NO_2 and *p*-Cl bearing) also cyclized efficiently and even reacted faster than electron-rich anilides (*p*-OMe and *p*-Me bearing), in contrast to most arylation processes proceeding *via* an S_EAr mechanism,[16] can be rationalized such that electrophilic palladation is not a kinetically prominent process in the course of cascade cyclization.

Based on the above results, a proposed mechanism is outlined in Scheme 4.[17] Anilide **1a** gives amidopalladation intermediate **A** in the presence of ligated Pd^{II} species. Upon *syn*-amidopalladation, σ-alkylpalladium species **B** is generated and the resulting Pd^{II} center activates the arene *via* resonance-stabilized **B-2** instead of following the counterion-assisted deprotonation process (**B-1**). The intermediacy of Pd^{II} species, instead of Pd^{IV}, is likely associated with the arene−activation step because of two reasons: (1) high reaction conversion from **1a** to **2a** was achieved with a stoichiometric amount of $Pd(OAc)_2$ under an argon atmosphere (oxygen-free); (2) cyclization of a monosubstituted alkene (**1v**) led to the enamide (**3v**) *via* a midway β-hydride elimination (eq 2), thereby ruling out the possibility of a Pd^{II}/Pd^{IV} catalytic manifold.[18] Subsequently, the second ring is closed through C−C bond-forming reductive elimination of palladacycle **C**. The catalytic cycle is completed by the regeneration of Pd^{II} from Pd^0 with molecular oxygen as the terminal oxidant.



In summary, we have demonstrated the broad scope of the Pd(II)-catalyzed intramolecular amidoarylation of alkenes that utilizes oxygen as a green oxidant. This work shows the bifunctionality (both nucleophilic and arylation site) of anilide as a simple building block to the construction of a range of common ring scaffolds. Elucidations of the cyclization mechanism provide the basis for further development of the enantioselective variant and a practical synthetic strategy toward the synthesis of alkaloids of biological interest.

Scheme 4. Plausible Mechanism



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Supporting Information Available. Experimental details; syntheses and characterization of **1a**−**u** and **2a**−**u**; determination of kinetic isotope effects. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) An alternative mechanism involving sequential C−H bond activation/carbopalladation of alkene/C−N bond formation is unlikely in our system because the bimolecular palladation of arenes is often assisted by protic acids. For example, see: ref 13d and Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066. In additon, successful oxidative triple cyclization (Scheme 3) also rules out this mechanism. We thank the reviewer for pointing out this possibility.

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